REMARKS/ARGUMENTS

The foregoing amendments in the specification and claims serve to identify the sequences recited by the corresponding sequence identification numbers, and do not add new matter. The Office Action mailed on March 30, 2001 (Paper No. 7) sets a one-month term. The present submission is accompanied by a request for a two-month extension of time, setting the new term to June 30, 2001.

Sequence Rule Compliance

Applicants were requested to comply with the sequence rules set forth in 37 C.F.R. §§1.821-1.825. The Sequence Listing filed concurrently herewith, the Sequence Submission Statement and the current amendments in the specification are believed to fully meet these requirements.

Election/Restriction Requirement

Applicants were requested to elect, for examination purposes, the invention of one Groups I - VI set forth on page 3 of the Office Action. In addition, upon the election of any of groups I-IV, applicants were further requested to elect one of the following "patentably distinct species:"

peptide species: 1) a peptide having an amino acid sequence corresponding to human p53, 2) a peptide having a motif FxxW, 3) an antibody capable of blocking a p53 binding site of mdm2, and 4) an antibody capable of blocking mdm2 binding site of p53;

conditions to be treated: 1) cancer; 2) viral condition, 3) other conditions;

and, if one of Groups V-VI is elected:

structures: 1) peptide, or 2) a fusion of a peptide;

delivery method: 1) microinjection into cells, or transport into cells.

In support of these requirements, the Examiner stated that the inventions listed as Groups I-VI do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features.

Applicants disagree and vigorously traverse the rejection. In order to be responsive, Group I (claims 1-9, and 11 drawn to a method of preventing or treating a condition comprising

disrupting the binding of human p53 and mdm2), the species of a peptide having an amino acid sequence corresponding to human p53, and the further species of cancer as the condition to be treated is elected, with traverse.

It is submitted that the restriction/election requirement is based on an improper interpretation of PCT Rules 13.1-13.3 and should be withdrawn. According to PCT Rule 13.1 *"The international application shall relate to one invention only or to a group of inventions so linked as to form a single general inventive concept."* (Emphasis added.) PCT Rule 13.2 provides: *"Where a group of inventions is claimed in one and the same international application, the requirement of unity of invention referred to in Rule 13.1 shall be fulfilled only when there is a technical relationship among those inventions involving one or more of the same or corresponding special technical features. The expression 'special technical features' shall mean those technical features that define a contribution which each of the claimed inventions, considered as a whole, makes over the prior art."* (Emphasis added.) Finally, according to PCT Rule 13.3, *"The determination whether a group of inventions is so linked as to form a single general inventive concept shall be made without regard to whether the inventions are claimed in separate claims or as alternatives within a single claim."*

The "single general inventive concept" underlying the present invention is the realization that mdm2 suppresses p53 not only in cells in which mdm2 is overexpressed, but also in cells in which it is not. All aspects of the invention share this inventive concept, as they all relate to reducing binding between mdm2 and p53, whether by disrupting that binding or by reducing the amount of mdm2 available to participate in binding. This is the contribution that each of the claimed inventions, considered as a whole, makes over the prior art, and this is why the International Preliminary Examining Authority, applying the same PCT Rules, found that the entire claim set met PCT unity requirements.

Although M.P.E.P. Section 1850 gives examiners a large degree of latitude in assessing the unity of an invention, dissection of a claim based upon the action mechanism by which an intended result is achieved, as the Examiner has done by treating the disruption of p53 and mdm2 binding and the inhibition of mdm2 production as separate and distinct inventions, is believed to

be at odds with well established practice of the USPTO, even as it applies to non-PCT originating, national U.S. applications. Accordingly, as a minimum, even under the strictest standards Groups I and II, Groups III and IV, and Groups V and VI should be examined in one application.

The election of species requirement is even less sustainable. The Examiner seems to have overlooked that claim 5 depends on claim 3, and therefore, concerns a peptide having an amino acid sequence corresponding to human p53 and additionally including an FxxxW (now referred to as FXaaXaaXaaW) motif. Accordingly, both peptides share the amino acid sequence of human p53, and should not be viewed as distinct species. Similarly, viewing a peptide and a fusion peptide as distinct species is contrary to settled practice. The same applies to treating microinjection and transport as distinct species, "because they work by different mechanisms."

In view of the foregoing arguments, applicant requests the reconsideration and withdrawal of the restriction and election of species requirements, and the examination of all claims pending in this application.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned "**Version with markings to show changes made**."

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410. A duplicate copy of this sheet is enclosed.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: June 11, 2001

By: _____

Ginger R. Dreger
Registration No. 33,055
Attorney of Record
620 Newport Center Drive
Sixteenth Floor
Newport Beach, CA 92660
(415) 954-4114

Version with markings to show changes made

In the Specification:

A Sequence Listing has been added to the specification, immediately following the claims.

The paragraph starting at page 2, line 12 has been amended as follows:

WO 96/02642 describes experiments to refine the peptide motif of p53 responsible for binding to mdm2, and shows that the motif is less extensive than disclosed in WO 93/20238. WO 96/02642 discloses that a [FccLW] FXaaXaaLW (SEQ ID NO: 1) motif between amino acid residues 18-23 of p53 (where [x] Xaa is any amino acid) is sufficient to bind to mdm2. This motif can be used to screen for therapeutic compounds capable of disrupting the interaction so that the transcriptional activity of p53 in cells overexpressing mdm2 can be restored.

The paragraph starting at page 7, line 9 has been amended as follows:

Variant peptides have an amino acid sequence which differs from wt p53 sequence, e.g. in the motif between amino acids 13-41 described in WO 96/02642, by one or more of addition, substitution, deletion and insertion of one or more amino acids, but which retains the activity of binding to mdm2. Such variants preferably include the motif [FxxxW] FXaaXaaXaaW (SEQ ID NO: 4), where [x] Xaa is any amino acids, and will typically share at least about 70%, more preferably at least about 80%, more preferably at least about 90%, or more preferably at least about 95% amino acid sequence identity with the corresponding portion of human p53. Examples of peptides capable of disrupting the interaction of p53 and mdm2 [and] are the thioredoxin insert peptides (TIPs) disclosed in Böttger et al, 1996, and in the examples below, see especially peptide TIP 12/1.

The paragraph starting at page 20, line 2 has been amended as follows:

pTrx (Invitrogen) was cleaved with RsrII. The following oligomers were phosphorylated, annealed and then ligated into the cleaved vector:

For TIP wt: 5' - 3'

GTCCGCCTCTGAGTCAGGAAACATTTTCAGACCTATGGAAACTACTTCCTGAAAACG (SEQ ID NO: 5)

and 5' - 3'

GACCGTTTTCAGGAAGTAGTTTCCATAGGTCTGAAAATGTTTCCTGACTCAGAGGCG (SEQ ID NO: 6)

For TIP 12/1: 5' - 3'

GTCCGCCTCTGAGTATGCCTCGTTTTATGGATTATTGGGAGGGTCTTAATGAAAACG (SEQ ID NO: 7)

and 5' - 3'

GACCGTTTTCATTAAGACCCTCCCAATAATCCATAAAACGAGGCATACTCTCAGAGG CG (SEQ ID NO: 8).

The sentence at page 20, lines 15-16 has been amended as follows:

The resulting peptide inserts are illustrated in Figure 1 (SEQ ID NOS: 2 and 3).

The paragraph starting at page 21, line 5 has been amended as follows:

For cloning of TIP 12/1, TIP wt and Trx into pcDNA3 for expression in mammalian cells, the thioredoxin coding region complete with the peptide insertions, was amplified from pTrx, pTrx 12/1 and pTrx wt using the following primers:

5' - 3': CGGGATCCACCATGGGCGATAAAATTATTCACCTG (SEQ ID NO: 9) and 5' - 3' CTCGACGCTAACCTGGCCTAGGGAATTCC (SEQ ID NO: 10).

The paragraph starting at page 24, line 16 has been amended as follows:

Construction of $F^{19} \rightarrow A$ was accomplished by site directed mutagenesis using the Transformer™ site directed mutagenesis kit (Clontech). The sequence of the selection primer was: 5' - 3' GACTCTGGGGATCGATATGACCGACC (SEQ ID NO: 11), the sequence of the mutagenic primer was: 5' - 3' GAGCCAGGAGACAGCCTCAGGCTTATG (SEQ ID NO: 12). The sequence of the p53 mutant $F^{19} \rightarrow A$ was confirmed by sequencing. --

In the Claims:

Claim 5 has been amended as follows:

5. (Twice amended) The method of claim 3 wherein the agent includes the peptide motif [FxxxW] FXaaXaaXaaW (SEQ ID NO: 4), where [x] Xaa is any amino acid.

Please amend claim 16 to read as follows:

16. (Twice amended) The method of claim 12 wherein the agent includes the peptide motif [FxxxW] FXaaXaaXaaW (SEQ ID NO: 4), where [x] Xaa is any amino acid.

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